USE OF XPERT MTB/RIF IN HIGH HIV PREVALENCE SETTINGS: WHAT HAVE WE LEARNT?


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Conflict of interest

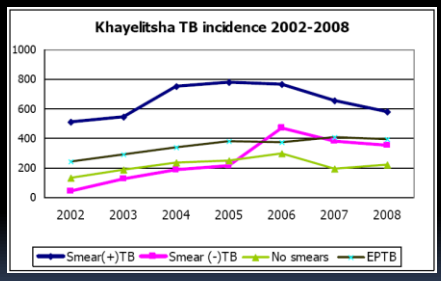
The University of Cape Town has received funding from FIND to support evaluation and demonstration studies for GeneXpert.

I have no other conflicts of interest to declare.

The context

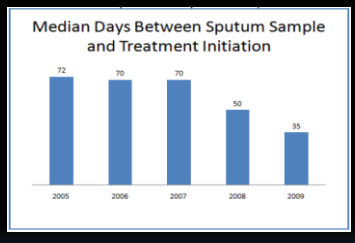
- Khayelitsha (Ubuntu clinic)
  - Antenatal HIV seroprevalence 31% in 2009 (70% TB patients)
  - TB incidence >1500/100 000 since 2005
  - On-site TB microscopy laboratory
- Paarl (6 clinics)
  - Antenatal HIV seroprevalence 12% in 2008 (40% TB patients)
  - TB incidence 680/100 000 in 2007
  - TB laboratory at district hospital


Diagnostic challenge: smear-negative TB



Khayelitsha Annual Activity Report 2008-2009 Médecins Sans Frontières, Western Cape Province Department of Health , City of Cape Town Department of Health, University of Cape Town, Centre for Infectious Disease Epidemiology and Research

Diagnostic challenge: delayed diagnosis of DR-TB



- From Jan 08 to June 09
  - 73 patients diagnosed with DR-TB did not start treatment.
  - 39/73 (53%) patients were known to have died whilst waiting for their results
  - median time of death was 25 days from sputum sampling.

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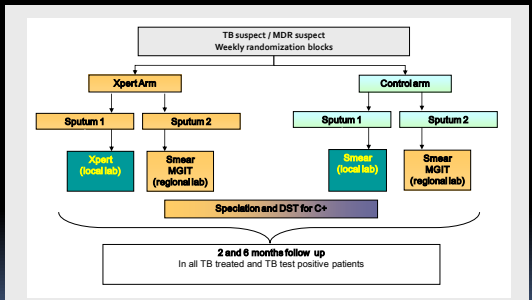
Cape Town Demo Study Design



What is in a lab?

- Both laboratory sites:
  - Fluorescent AFB microscopy
  - NHLS QA programme

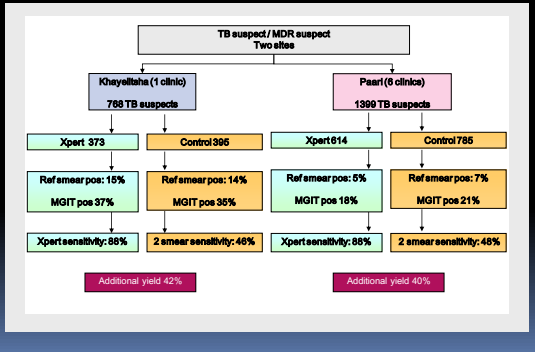
KY clinic laboratory
- started operation 1 month prior to study
- Single experienced technician
- 40-50 smears per day

vs.

Paarl laboratory
- Established district laboratory
- 2 staff members performing/reading AFB smears
- 200 smears per day (multiple clinics)

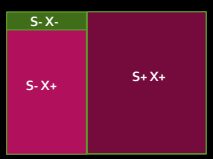
Same Xpert training provided to both

Cape Town Demo Study: Summary

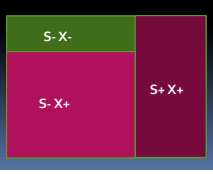


Impact of HIV on performance of smear microscopy and Xpert

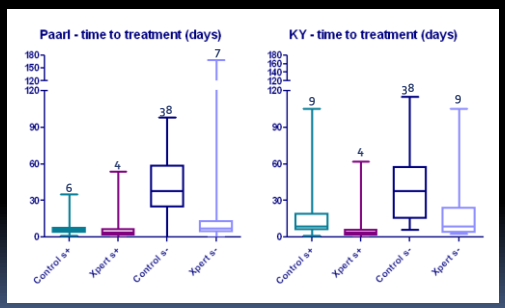
- Sensitivity of Xpert:
  - HIV-negative patients
    - All HIV neg: 95%
    - Smear pos: 100%
    - Smear neg: 92%



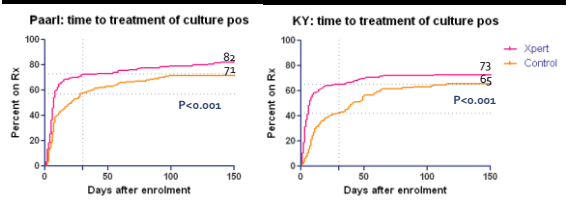
  - HIV-infected patients
    - All HIV pos: 85%
    - Smear pos: 100%
    - Smear neg: 79%



Time to treatment



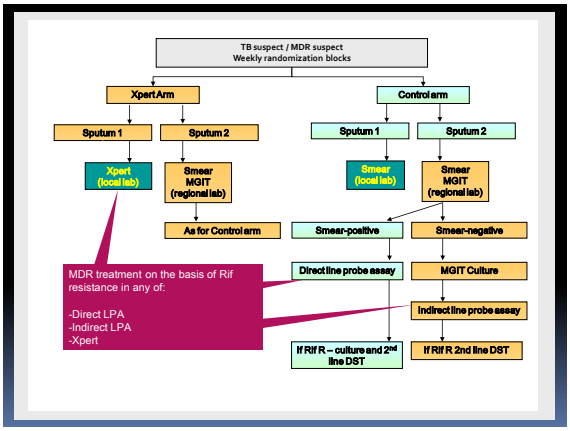
Time to treatment



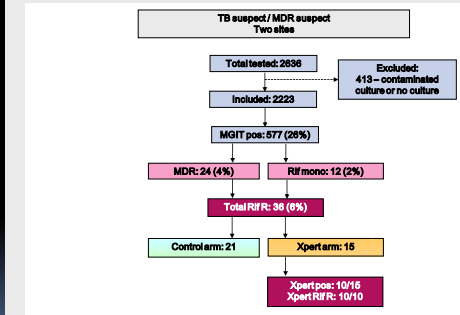
Mortality:
KY: 5 deaths in culture-positive patients:
all in control arm (NS)
3 not started on TB treatment
2 started on treatment (at 9 and 16 days)

Performance of Xpert for detection of Rif resistance

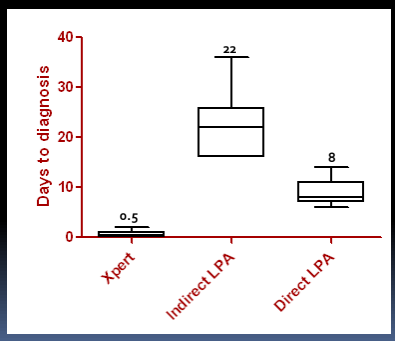
- Evaluation study
  - Comparison with phenotypic DST:
    - sensitivity 98% specificity 98%
  - After sequencing discordant isolates
    - sensitivity 99% specificity 100%



Cape Town Demo Study: Summary



Comparison of time to detection



Performance of Xpert for detection of Rif resistance

- Evaluation study
  - Comparison with phenotypic DST:
    - sensitivity 98% specificity 98%
  - After sequencing discordant isolates
    - sensitivity 99% specificity 100%
- Early demonstration study
  - 2 cases identified in Khayelitsha
    - Rif R on Xpert, Rif S on LPA (confirmed WT on sequencing)
  - Subsequently 2 cases identified in Paarl, other sites
  - Sensitivity 99 (96-100) % specificity 96 (95-97) %
    205/208 (679/706)

Prevalence of MDR and PPV

	Positive Predictive Value		
		Specificity 96%	Specificity 98%
Prevalence of RIF resistance	5%	56	71
	10%	73	84
	20%	86	92
	50%	96	98

Development of an improved assay

- Identification of cause of problem:
  - 1. Clumping of specific probes prior to cartridge loading (age-related)
  - 2. Poor binding of one of probes to target DNA at high operating temperatures (within instrument)
- Fix:
  - 1. Software change to improve re-suspension steps
  - 2. Redesign of one probe to improve annealing at high temperatures
- Clinical testing early 2011

Conclusions

- Significant advantages over smear microscopy:
  - Additional yield of Xpert over 2 concentrated smears: 40-42%
  - Incremental benefit equivalent in medium and high HIV-prevalence communities
  - Less variability in performance than smear microscopy
  - Time to treatment of smear neg TB reduced by 1 month
- Major limitation of this study: culture included for all suspects
  - Need to assess performance against standard diagnostic algorithm
  - Is the data compelling enough? Local cost-benefit analysis – but current outcome data likely to underestimate impact

Conclusions

Use of Xpert in low/moderate MDR prevalence settings:

- Substantial reduction in time to detection of RIF resistance
- Current assay version:
  - High NPV for RIF resistance
    - Excellent screening tool to exclude RIF resistance
  - Relatively lower PPV
    - Need confirmatory testing of resistant calls
    - Defined treatment strategy whilst awaiting confirmation
    - Access to second-line rapid diagnostics (e.g. LPA) and culture
    - Education of health care workers
- New assay this year

Acknowledgements

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